Biomarker-Guided Versus Guideline-Based Treatment of Patients With Heart Failure

Ouwerkerk, Wouter; Zwinderman, Aeilko H.; Ng, Leong L.; Demissei, Biniyam; Hillege, Hans L.; Zannad, Faiez

Published in:
Journal of the American College of Cardiology

DOI:
10.1016/j.jacc.2017.11.041

Publication date:
2018

Online Appendix

Online Table 1. Summary statistics of biomarkers.

	Mean (SD) or median (interquartile range)	% Missing
Standard laboratory results		
Hematocrit (%)	39.46 (±5.24)	6%
Total Cholesterol (mmol/L)	3.35 (±1.36)	40%
Serum Creatinine (umol/L)	486.21 (466.77-509.91)	0%
BUN (mmol/L)	28.03 (23.34-33.61)	13%
NT Pro-BNP (ng/L)	32877.72 (30507.05-35607.69)	55%
Hemoglobin (g/dL)	12.5 (11.2-13.6)	4%
Sodium (mmol/L)	138.29 (±3.75)	2%
Potassium (mmol/L)	3.27 (±0.55)	2%
BNP (pg/mL)	3974.99 (3480.72-4349.76)	88%
Total Bilirubin (umol/L)	38.15 (33.08-43.78)	39%
Glucose (mmol/L)	12.21 (11.26-13.77)	20%
LDL (mmol/L)	1.64 (±1.08)	53%
HDL (mmol/L)	0.1 (±0.38)	51%
Serum Iron (umol/L)	28.47 (24.09-32.13)	78%
Calcium (mmol/L)	0.96 (0.7-1.17)	4%
Phosphate (mmol/L)	-0.13 (-0.32-0.02)	4%
Albumin (g/L)	107.72 (102.65-112.06)	4%
Serum iron (ug/L)	16.75 (12.57-20.03)	4%
Ferritin (ug/L)	441.47 (372.63-501.29)	4%
Transferrin (g/L)	1.33 (0.9-1.75)	4%
HEPC	10.97 (4.55-16.41)	4%
Soluble Transferrin Receptor (mg/L)	0.62 (0.2-1.1)	5%
Free Thyroxine (FT4) pmol/L)	44.01 (41.2-46.65)	76%
HbA1c (%)	11.74 (11.18-12.59)	78%
ASAT (U/L)	87.72 (77.21-99.31)	23%
ALAT (U/L)	87.99 (80.49-97.19)	30%
TSH (mU/L)	1.01 (0.27-1.74)	60%
Proteinuria (mg/dL)	10.07 (3.59-15.8)	90%
Gamma-GT (U/L)	223.88 (187.01-260.12)	48%
Alkaline Phophatase (ug/L)	392.05 (369.06-421.48)	47%
TnI (pg/mL)	37.95 (28.69-49.42)	3%
ET-1 (pg/mL)	8.79 (7.29-10.33)	3%
pro-ENK (pmol/L)	387.98 (362.33-415.26)	0%
bio-ADM (pg/mL)	122.81 (109.63-138.52)	0%
Troponin (ug/L)	-0.14 (-0.18--0.09)	72%
FGF23 (RU/ml)	1484.76 (1324.41-1733.13)	0%

Erythrocytes (10e12/L)	6.67 (6.25-7.05)	26%
Platelets (10e9/L)	1140.11 (1094.92-1179.84)	18%
Leucocytes (10e9/L)	16.02 (14.5-17.47)	17%
Alere Luminex Panel		
ANP propeptide (ng/ml)	55.93 (46.94-64.06)	3%
BNP (pg/mL)	1039.89 (857.4-1179.9)	3%
ESAM-1 (ng/ml)	62.84 (±10.88)	3%
LTBR (ng/ml)	-0.83 (±0.11)	3%
Mesothelin (ng/ml)	53.42 (±12.64)	3%
MPO (ng/ml)	30.7 (±15.08)	3%
Neuropilin (ng/ml)	20.61 (±7.68)	3%
NT-ProCNP (pg/ml)	14.53 (14.53-23)	3%
Osteopontin (ng/ml)	217.2 (±63.62)	3%
PCT (pg/ml)	48.32 (30.66-63.02)	3%
PSAP_B (ng/ml)	29.52 (±11.47)	3%
VEGFR1 (ng/ml)	-0.38 (-0.38--0.28)	3%
D-dimer (ng/ml)	643.55 (643.55-683.1)	3%
Pentraxin-3 (ng/ml)	1.4 (0.32-2.46)	3%
PIGR (ng/ml)	578.73 (522.28-638.38)	3%
RAGE (ng/ml)	2.73 (1.74-3.78)	3%
Syndecan-1 (ng/ml)	1.57 (0.22-2.77)	3%
TNFR1A (ng/ml)	-0.02 (-0.53-0.47)	3%
Troy (ng/ml)	-0.34 (-0.47--0.21)	3%
GDF-15 (ng/ml)	2.6 (±1.31)	3%
pro-ADM (ng/ml)	-0.36 (-0.58--0.14)	3%
ST2 (ng/ml)	17.03 (10.78-23.51)	3%
WAP4C (ng/ml)	0.45 (-0.45-1.51)	3%
Periostin (ng/ml)	10.36 (7.2-13.25)	3%
Angiogenin (ng/ml)	41368.43 (39515.51-43485.06)	3%
Cystatin C (ng/ml)	140287.4 (134889.27-145859.04)	3%
CRP (ng/ml)	107543.9 (98053.65-115527.45)	3%
GAL-3 (ng/ml)	65.08 (58.25-71.96)	3%
NGAL (ng/ml)	241.82 (215.61-269.05)	3%
Olink Proseek Multiplex panel		
NPX TNFRSF14	5.79 (±0.86)	0%
NPX LDL receptor	3.02 (±1.01)	0%
NPX ITGB2	6.36 (±0.8)	0%
NPX IL-17RA	3.64 (±0.75)	0%
NPX TNF-R2	6.13 (±0.89)	0%
NPX MMP 9	3.1 (±1.11)	0%
NPX EPHB4	0.49 (±0.53)	0%

NPX IL2-RA	4.47 (±0.84)	0%
NPX OPG	2.61 (±1.06)	0%
NPX ALCAM	5.66 (±0.67)	0%
NPX TFF3	8.36 (±0.91)	0%
NPX SELP	17.07 (±1.13)	0%
NPX CSTB	6.89 (±0.78)	0%
NPX MCP-1	2.07 (±0.8)	0%
NPX CD163	12.79 (±0.83)	0%
NPX GAL-3	6.42 (±0.73)	0%
NPX GRN	4.37 (±1.01)	0%
NPX MEPE	1.5 (±0.78)	0%
NPX BLM hydrolase	6.69 (±0.63)	0%
NPX PLC	11.74 (±0.78)	0%
NPX LTBR	3.05 (±0.77)	0%
NPX NOTCH-3	3.46 (±0.81)	0%
NPX TIMP4	6.43 (±0.87)	0%
NPX CNTN1	1.94 (±1.08)	0%
NPX CDH5	2.55 (±0.76)	0%
NPX TLT-2	4.15 (±0.81)	0%
NPX FABP4	8.31 (±1.32)	0%
NPX TFPI	15.54 (±0.77)	0%
NPX PAI	7.41 (±1.26)	0%
NPX CCL24	7.26 (±1.12)	0%
NPX TR	7.86 (±0.86)	0%
NPX TNFRSF10C	8.48 (±0.82)	0%
NPX GDF-15	7.52 (±1.06)	0%
NPX SELE	1.89 (±1.15)	0%
NPX AZU1	1.37 (±0.71)	0%
NPX DLK-1	5.73 (±0.98)	0%
NPX SPON1	0.72 (±0.56)	0%
NPX MPO	4.23 (±0.72)	0%
NPX CXCL16	9.24 (±0.7)	0%
NPX IL 6RA	23.19 (±0.69)	0%
NPX RETN	10.46 (±0.86)	0%
NPX IGFBP-1	6.33 (±1.56)	0%
NPX CHIT1	4.08 (±5.75)	0%
NPX TR-AP	6.14 (±0.7)	0%
NPX CCL22	0.18 (±1.42)	0%
NPX PSP-D	1.29 (±0.77)	0%
NPX PI3	3.66 (±0.72)	0%
NPX EP CAM	2.78 (±1.01)	0%
NPX AP-N	5.98 (±0.77)	0%
NPX AXL	13.71 (±0.74)	0%

NPX IL-1RT1	10.13 (±0.73)	0%
NPX MMP 2	3.62 (±1.09)	0%
NPX FAS	5.72 (±0.74)	0%
NPX MB	11.1 (±0.97)	0%
NPX TNFSF13B	8.81 (±0.8)	0%
NPX PRTN3	5.35 (±0.74)	0%
NPX PCSK9	0.96 (±0.59)	0%
NPX U-PAR	5.5 (±0.78)	0%
NPX OPN	7.2 (±1.09)	0%
NPX CTSD	3.57 (±0.67)	0%
NPX PGLYRP1	12.17 (±0.85)	0%
NPX CPA1	4.44 (±1.65)	0%
NPX JAM-A	6.74 (±1.18)	0%
NPX GAL-4	3.05 (±0.85)	0%
NPX IL 1RT2	5.44 (±0.7)	0%
NPX SHPS 1	2.94 (±0.73)	0%
NPX CCL15	12.14 (±0.81)	0%
NPX CASP-3	12.27 (±1.69)	0%
NPX UPA	5.07 (±0.74)	0%
NPX CPB1	4.84 (±1.31)	0%
NPX CHI3L1	9.31 (±1.22)	0%
NPX ST2	4.61 (±1.03)	0%
NPX T-PA	7.65 (±1.43)	0%
NPX SCGB3A2	1.2 (±1.1)	0%
NPX EGFR	0.15 (±1.04)	0%
NPX IGFBP-7	4.52 (±0.96)	0%
NPX CD93	19.22 (±0.71)	0%
NPX IL 18BP	9.66 (±0.78)	0%
NPX COL1A1	2.29 (±0.88)	0%
NPX PON3	5.69 (±1.37)	0%
NPX CTSZ	5.72 (±0.76)	0%
NPX MMP 3	12.53 (±1.01)	0%
NPX RARRES2	26.2 (±0.63)	0%
NPX ICAM 2	5.99 (±0.76)	0%
NPX KLK6	2.69 (±0.41)	0%
NPX PDGF subunit A	0.84 (±1.69)	0%
NPX TNF-R1	7.69 (±0.76)	0%
NPX IGFBP-2	15.16 (±0.97)	0%
NPX VWF	10.5 (±1.47)	0%
NPX PECAM 1	6 (±0.93)	0%
NPX NT-pro BNP	2.49 (±1.39)	0%
NPX CCL16	8.79 (±0.93)	0%

Online Table 2. Most frequently selected biomarkers predictive for death and/or heart failure hospitalization in patients who were successfully up-titrated to >50% of recommended ACE-inhibitor/ARB dose or not.

Uptitrated patients	selected in number of training sets	log(Hazard Ratio) (SE)
BUN (mmol/L)	96	0.19 (0.0099)
FGF-23 (RU/mL)	95	0.13 (0.0073)
proENK (pmol/L)	67	0.11 (0.0092)
Ferritin (mg/L)	61	-0.1 (0.0082)
Troponin I (pg/mL)	58	0.14 (0.0121)
ESAM1 ng/ml)	56	0.07 (0.0073)
NGAL (ng/mL)	55	0.08 (0.0088)
Phosphate (mmol/L)	49	-0.11 (0.0101)
NT-proBNP (NPX)	47	0.08 (0.0087)
Cystatin C (ng/mL)	46	0.09 (0.0085)
CHIT1 (NPX)	41	-0.08 (0.0079)
FABP4 (NPX)	40	0.1 (0.0121)
Total cholesterol (mmol/L)	34	-0.16 (0.0201)
Sodium (mg/dL)	32	-0.09 (0.0103)
CSTB (NPX)	32	0.09 (0.0102)

NOT Uptitrated patients	selected in number of training sets	log(Hazard Ratio) (SE)
FGF-23 (RU/mL)	100	0.15 (0.0047)
BUN (mmol/L)	99	0.1 (0.0044)
Cystatin C (ng/mL)	96	0.1 (0.0043)
ST2 (NPX)	86	0.1 (0.0068)
WAP-4C (ng/mL)	84	0.09 (0.0056)
IGFBP 2 (NPX)	83	0.07 (0.0052)
Bio-ADM (pg/mL)	78	0.05 (0.003)
HDL-cholesterol (mmol/L)	71	-0.07 (0.0052)
LDL RECEPTOR (NPX)	70	-0.08 (0.0062)
HB (g/dL)	68	-0.07 (0.0047)
Troponin I (pg/mL)	68	0.05 (0.0033)
ST2 (ng/mL)	67	0.08 (0.0068)
Alkaline phosphatase (ug/mL)	64	0.04 (0.0033)
NT-proBNP (ng/L)	63	0.06 (0.0048)
ASAT (U/L)	63	-0.04 (0.0035)

Online Table 3. Most frequently selected biomarkers predictive for death and/or heart failure hospitalization in patients who were successfully up-titrated to >50% of recommended beta-blocker dose or not.

Uptitrated patients	**selected in number of training**	**log(Hazard Ratio) (SE)**
Serum creatinine (umol/L)	95	0.22 (0.014)
Gal-3 (ng/mL)	95	0.27 (0.0103)
ST2 (ng/mL)	89	0.16 (0.0097)
Albumin (g/L)	83	-0.25 (0.0128)
Hematocrit (%)	69	-0.15 (0.0136)
IGFBP 2 (NPX)	66	0.17 (0.0172)
EP-cam (NPX)	60	0.16 (0.0187)
Cystatin C (ng/mL)	59	0.13 (0.0142)
MMP 3 (NPX)	57	0.1 (0.0109)
Phosphate (mmol/L)	56	-0.23 (0.0251)
NT-proBNP (ng/L)	50	0.15 (0.014)
Hepcidin (nmol/L)	49	-0.12 (0.0113)
BUN (mmol/L)	46	0.18 (0.0212)
LVEF (%)	41	0.11 (0.0116)
Potassium (mmol/L)	40	0.07 (0.0091)

NOT Uptitrated patients	selected in number of training	log(Hazard Ratio) (SE)
FGF-23 (RU/mL)	100	0.19 (0.0044)
Cystatin C (ng/mL)	100	0.12 (0.0042)
BUN (mmol/L)	99	0.11 (0.0042)
WAP-4C (ng/mL)	99	0.13 (0.0055)
NT-proBNP (NPX)	94	0.08 (0.0038)
Troponin I (pg/mL)	79	0.06 (0.0031)
TNFSF13B (NPX)	79	0.06 (0.0043)
PI3 (NPX)	74	0.05 (0.0035)
ST2 (NPX)	72	0.06 (0.005)
HDL-cholesterol (mmol/L)	71	-0.06 (0.004)
Bio-ADM (pg/mL)	71	0.04 (0.004)
LDL RECEPTOR (NPX)	70	-0.08 (0.0052)
HB (g/dL)	65	-0.04 (0.0041)
SCGB3A2 (NPX)	62	0.05 (0.0044)
U-par (NPX)	57	0.06 (0.0059)

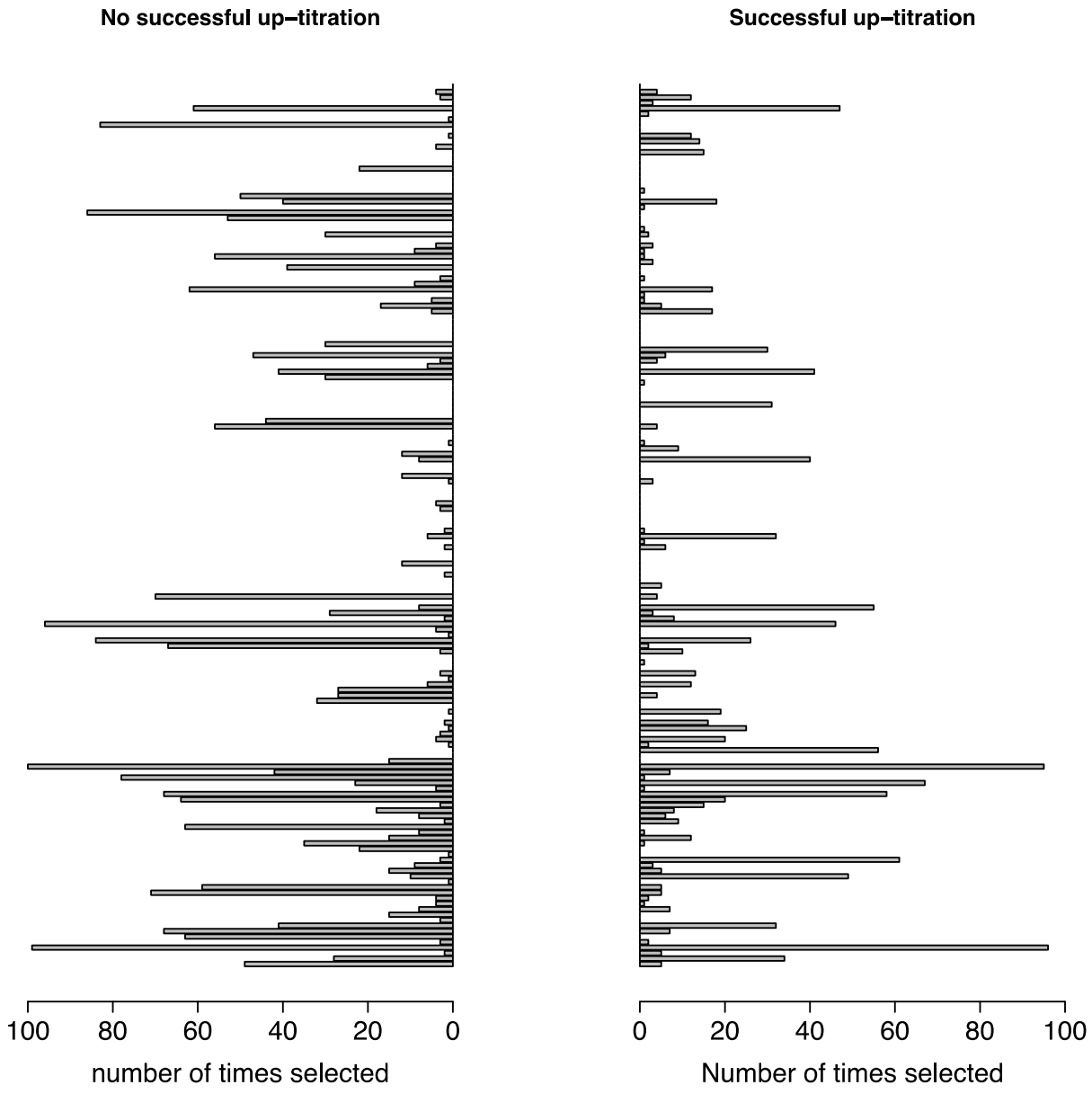
Online Table 3. Most frequently selected biomarkers predictive for death and/or heart failure hospitalization in patients who were successfully up-titrated to ≥50% of recommended MRA dose or not.

Uptitrated patients	**selected in number of training sets**	**log(Hazard Ratio) (SE)**
Potassium	57	-0.41 (0.0229)
PI3 (NPX)	52	0.28 (0.0147)
Bio-ADM	25	0.16 (0.0392)
CCL22 (NPX)	20	-0.14 (0.0163)
AXL (NPX)	13	0.15 (0.0266)
IGFBP 2 (NPX)	11	0.16 (0.0206)
HDL-cholesterol (mmol/L)	10	0.16 (0.0363)
ESAM-1 (ng/mL)	10	0.14 (0.0415)
ET1 (pg/mL)	7	0.15 (0.075)
Proteinuria (mg/dL)	6	0.27 (0.0649)
Gamma GT (mU/L)	6	0.19 (0.0614)
Phosphate (mmol/L)	5	-0.16 (0.0531)
Leucocytes (10^9/L)	5	-0.09 (0.0415)
BNP (pg/mL)	4	0.11 (0.0433)
LDL-cholesterol (mmol/L)	4	-0.1 (0.0284)

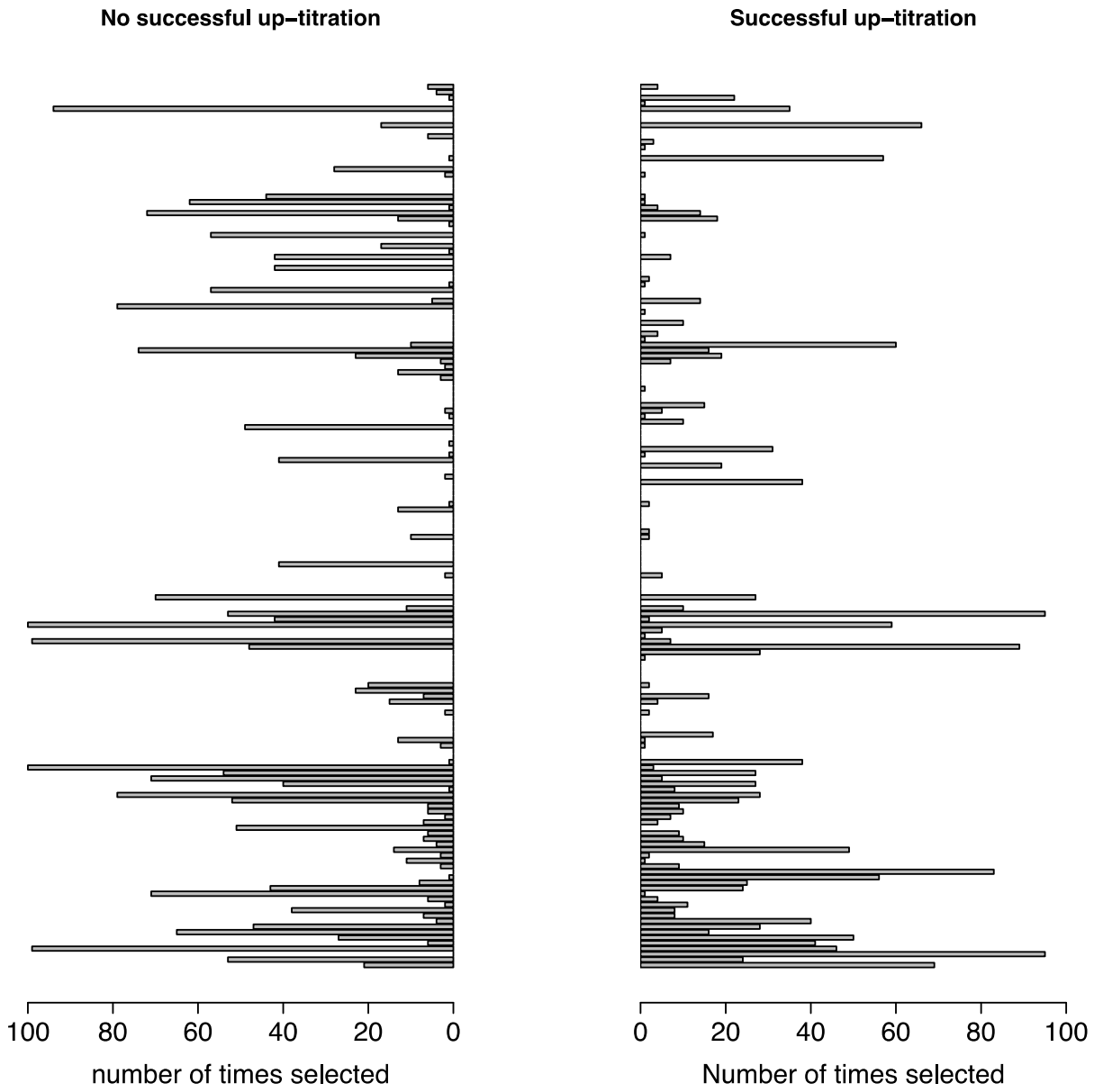
NOT uptitrated patients	selected in number of training sets	log(Hazard Ratio) (SE)
PRTN3 (NPX)	100	0.16 (0.0058)
Cystatin C (ng/mL)	99	0.14 (0.0043)
NGAL (ng/mL)	99	0.09 (0.0044)
BUN (mmol/L)	95	0.09 (0.0057)
GAL 4 (NPX)	94	0.11 (0.0069)
ST2 (ng/mL)	90	0.09 (0.0052)
PIGR-1 (ng/mL)	86	0.09 (0.0052)
CHIT1 (NPX)	82	-0.08 (0.0044)
TNI (ug/L)	81	0.06 (0.0043)
pro-ENK (pmol/L)	77	0.07 (0.0049)
ASAT (U/L)	76	-0.06 (0.0047)
NT-proBNP (ng/L)	75	0.11 (0.0063)
Erythrocytes (10^12/L)	74	-0.07 (0.0057)
CPA1 (NPX)	71	-0.1 (0.0051)
FGF-23 (RU/L)	69	0.07 (0.0054)

Online Figures

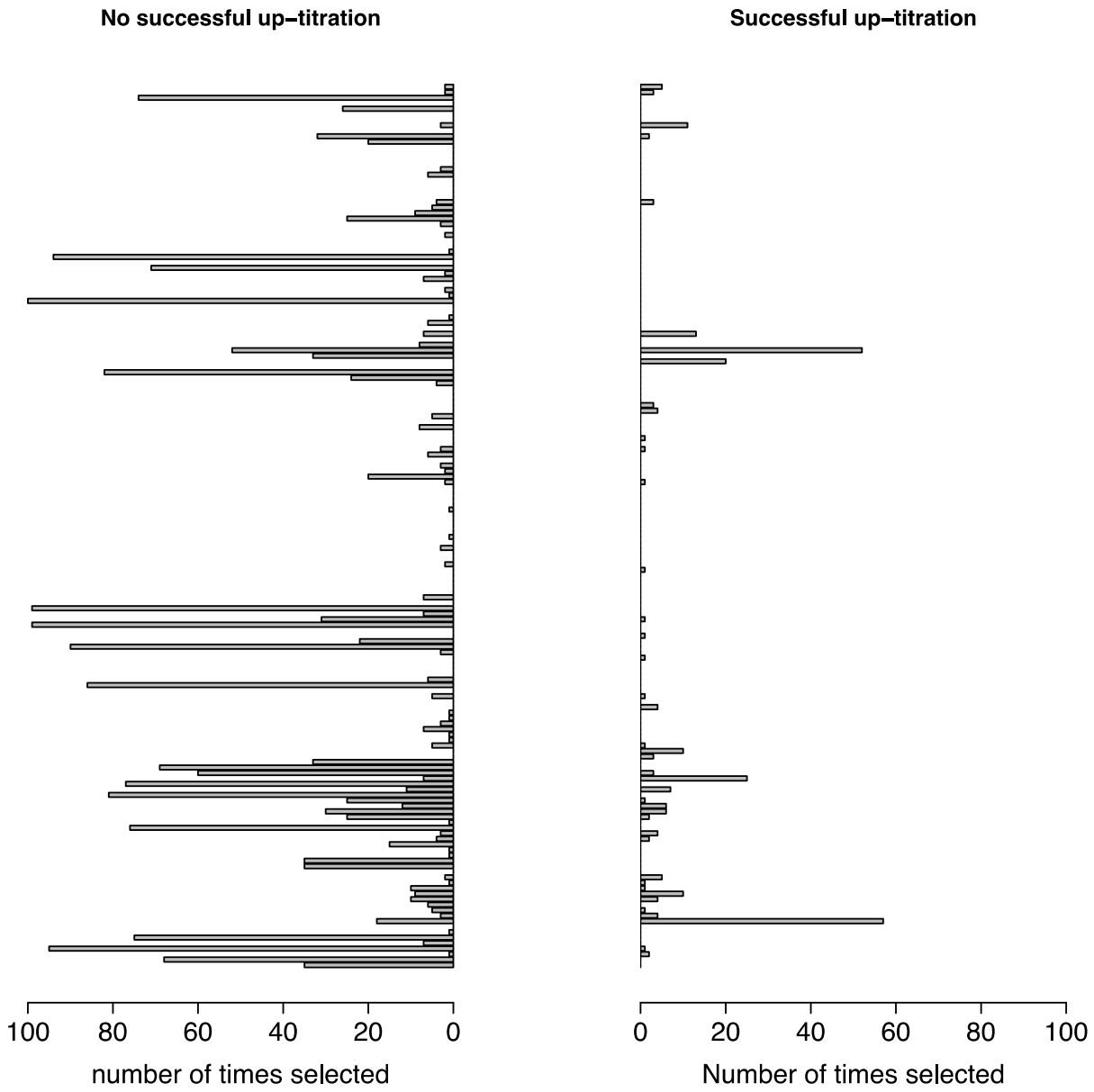
Online **Figure 1.** Selection frequency of the 161 biomarkers in the multivariable Cox regression models for patients up-titrated and not up-titrated to >50% of recommended ACE-inhibitor/ARB dose. On the x-axes the number of times a marker was selected is displayed, on the y-axes the 161 biomarkers were ordered.



Online Figure 2. Selection frequency of the 161 biomarkers in the multivariable Cox regression models for patients up-titrated and not up-titrated to >50% of recommended beta-blocker dose. On the x-axes the number of times a marker was selected is displayed, on the y-axes the 161 biomarkers were ordered.



Online Figure 3. Selection frequency of the 161 biomarkers in the multivariable Cox regression models for patients up-titrated and not up-titrated to ≥50% of recommended MRA dose. On the x-axes the number of times a marker was selected is displayed, on the y-axes the 161 biomarkers were ordered.



Online Appendix Data

Biomarkers

There were 21,184 missing values in total on all biomarkers in the 1802 remaining patients and this was about 7% of all biomarker values (161 biomarkers x 1802 patients). The percentage of missing biomarkers per patient is presented in Online Figure 1. Of the 1802 patients included in this study 26 (1%) had more that 25% missing biomarkers. Of the included patients 249 (14%) had missing biomarker values between 25% and 10%. Roughly half the patient population had less than 7% missing biomarkers. There were no major differences between patients missing less than 7% and more than 7%, as presented in Online Table 1, patients missing more than 7% of biomarkers were slightly older female, had lower heart rate, more frequent peripheral artery disease and COPD, and lower BUN levels.

The missing biomarker measurements were multiply imputed five times. Several standard biochemical biomarkers, and markers from the Alere platform showed highly skewed distributions and these were all *log*-transformed using natural logs . Only hematocrit, hemoglobin, sodium, potassium, LVEF, total-, LDL- and HDL-cholesterol, ESAM-1, LTBR, mesothelin, MPO, neuropilin, osteopontin, PSAP-B, and GDF-15 were analysed on the original scale. All biomarkers were successfully standardized before further analysis.

Prediction of up-titration-success at three months follow-up

Of the 1802 patients, 529 (29%) were up-titrated to >50% of recommended ACE-inhibitor/ARB dose and 318 (18%) to >50% of recommended beta-blocker dose. Biographical and clinical characteristics of the patients up-titrated to >50% of recommended ACE-inhibitor/ARB and beta-blocker dose or not are listed in **Table 1.** Patients up-titrated to >50% of recommended ACE-inhibitor/ARB dose were younger and heavier, had higher blood pressure,

less frequent hepatomegaly and a better kidney function. Patients up-titrated to >50% of recommended beta-blocker dose had higher blood pressure, and heart rate, and lower BUN.

Logistic regression with a lasso penalty selected 33 markers that were predictive for successfully up-titrated to >50% of recommended ACE-inhibitor/ARB dose in at least one of the five imputed datasets (Online Table 2). Of these 33 markers, the following 20 markers were selected in all five imputed sets; valvular disease, diabetes mellitus, hypertension, renal disease, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulmonary congestion, body mass index, serum creatinine, BUN, sodium, TNI, pro-ENK, FGF23, WAP-4C, TR,ep-CAM and ST2. The 25 strongest independent predictors of successful up-titration of beta-blockers were sex, age, valvular disease, previous heart failure related hospitalization in year before inclusion, ischemic etiology, atrial fibrillation, alcohol usage, stroke, device therapy, height, weight, heart rate, DBP, pulmonary congestion, third heart tone, orthopnea, ASAT, PSAP-B, D-dimer, periostin, EPHB4, TR, MMP-2 , PDGF subunit A and smoking in the past (Online Table 3). Probabilities of being up-titrated to recommended treatment dose varied, in both ACE-inhibitor/ARB and beta-blockers models, between zero and one in both the patients who were successfully up-titrated and in patients who were not actually successfully up-titrated for ACE-inhibitors/ARB's and beta-blockers. Mean probabilities for patients up-titrated to >50% of recommended ACE-inhibitor/ARB and beta-blocker dose were 0.37 (SD 0.15) and 0.27 (SD 0.15) and 0.26 (SD 0.14) and 0.16 (SD 0.10) for patients not up-titrated to recommended dose, respectively (Online Figures 2 and 3).

For MRA's we had information for 1423 patients at 9 months after inclusion. Of these patients, 28 achieved >50% of recommended MRA treatment and 195 achieved ≥50% recommended MRA treatment dose. Patients up-titrated to achieved ≥50% recommended MRA

treatment dose Online Table 4. Mean probabilities for patients being up-titrated to ≥50% recommended MRA dose was 0.30 (SD 0.20) and 0.11 (SD 0.11) for patients who were non-responders (Online Figure 4).

Optimism corrected c-statistics were 0.68 for ACE-inhibitors/ARB's and 0.69, for beta-blockers, averaged over the five imputed datasets. Highest optimism c-statistics (0.74) were found in the MRA up-titration.

There were relatively few patients who were not successfully up-titrated with propensities > 0.8, and likewise there were relatively few patients who were successfully up-titrated with propensities < 0.1. This unbalance might bias our results and we therefore performed all analyses also using only the patients with propensity for successful up-titration between 0.1 and 0.8. Results did not change much and we therefore only report results using data of all 1802 patients.

The proportional hazards assumption for the linear effect of biomarkers on mortality and/or heart failure hospitalization-risk seemed to apply to all biomarkers. No markers for the ACE-inhibitors/ARB's multivariate treatment-selection models and seventeen markers for beta-blockers had a *p*-value of the Grambsch-Therneau-test less than 0.05, but none had *p*-value<0.05 after Bonferroni correction.

The Kaplan-Meier survival curves of patients, who were and were not successfully up-titrated to >50% recommended ACE-inhibitors/ARB's doses are given in Online Figure 5. There was a clear and significant ($p<0.00001$, hazard ratio (HR) = 0.59, 95% CI 0.46-0.76) advantage for patients who were up-titrated successfully to >50% recommended dose for ACE-inhibitors/ARB's. With respect to beta-blocker treatment there was no significant difference in survival (0.75, 95% CI 0.56-1.01, $p=0.06$).

After inverse propensity weighting, there was no significant benefit for those who were up-titrated recommended dose (Online Figures 5 and 6).

The Kaplan-Meier survival curves of patients, who were and were not up-titrated to ≥50% recommended MRA doses are given in Online Figure 7. There was no significant difference in survival between responders and non-responders before (HR 0.78 (95% CI 0.48-1.26); p=0.31) and after inverse propensity weighting (HR 0.84 (95% CI 0.0.67-1.05); p=0.13)

Online Table 1. Patient characteristics of patients with more or less 25% biomarkers missing

	more than 25 % missing	less than 25 % missing	P-value
Number of patients: n (%)	26	1776	
% of recommended ACE-inhibotor/ARB dose: mean (SD)	46 (37)	50 (39)	
% of recommended beta-blocker dose: mean (SD)	36 (29)	37 (31)	
Age (years): mean (SD)	69.45 (12.84)	67.6 (12.05)	0.47
Male gender: n (%)	18 (69%)	1344 (76%)	0.45
Caucasian ethnicity: n (%)	26 (100%)	1756 (99%)	0.96
BMI (kg/m2): mean (SD)	28.67 (5.24)	27.9 (5.53)	0.48
Systolic blood pressure: mean (SD)	120.19 (19.26)	123.87 (21.47)	0.34
Diastolic blood pressure (mmHg): mean (SD)	73.42 (12.95)	75.27 (13.16)	0.48
Heart rate (bpm): mean (SD)	84.27 (18.01)	79.88 (19.54)	0.23
Smoking (current/ever/never): n	13/8/5	634/878/264	0.17
Alcohol use: n (%)	16 (62%)	1261 (71%)	0.29
Ischemic HF etiology: n (%)	17 (65%)	807 (45%)	0.04
HF duration (years): median (IQR)	0.18 (0.18-0.18)	8.02 (3.54-13.31)	0.1
NYHA class III/IV: n (%)	11 (42%)	742 (42%)	0.96
LVEF: median (IQR)	29 (21-34)	29 (24-34)	0.59
NT-proBNP, ng/L: median (IQR)	33876 (31812-35503)	32868 (30502-35612)	0.39
Oedema, % (n)	14 (54%)	817 (46%)	0.43
Orthopnoea, % (n)	10 (38%)	571 (32%)	0.5
Rales >1/3 up lung fields, % (n)	2 (13%)	167 (19%)	0.58
Jugular venous pressure, % (n)	7 (35%)	385 (30%)	0.64
Hepatomegaly, % (n)	1 (4%)	243 (14%)	0.14
Hypertension, % (n)	13 (50%)	1067 (60%)	0.3
Atrial fibrillation, % (n)	13 (50%)	760 (43%)	0.46
Myocardial infarction, % (n)	5 (19%)	674 (38%)	0.05
PCI, % (n)	5 (19%)	386 (22%)	0.76
CABG, % (n)	3 (12%)	287 (16%)	0.52
None	20 (1%)	1339 (74%)	0.98
Pacemaker only	2 (0%)	115 (6%)	
ICD only	2 (0%)	150 (8%)	
CRT only	0 (0%)	35 (2%)	
ICD and CRT	2 (0%)	131 (7%)	
Other	0 (0%)	6 (0%)	
Diabetes mellitus, % (n)	7 (27%)	564 (32%)	0.6
COPD, % (n)	5 (19%)	285 (16%)	0.66
Stroke, % (n)	2 (8%)	160 (9%)	0.82
Peripheral artery disease, % (n)	4 (15%)	184 (10%)	0.41
Aldosterone antagonists, % (n)	15 (58%)	971 (55%)	0.76
Loop diuretics, % (n)	26 (100%)	1768 (100%)	0.73
Digoxin, % (n)	8 (31%)	316 (18%)	0.09
Haemoglobin, g/dL: mean (SD)	12.53 (1.62)	12 (2)	0.65
Creatinine, Œmol/L: median (IQR)	483 (467-513)	486 (467-510)	0.9
BUN, mmol/L: median (IQR)	29.2 (23.3-33.3)	28 (23-34)	0.68
GFR MDRD formula, mL/min.1.73m2: mean (SD)	66 (28)	66 (23)	0.91
Sodium, mmol/L: mean (SD)	139.77 (2.93)	138.27 (3.76)	0.02
Potassium, mmol/L: mean (SD)	3.22 (0.59)	3.27 (0.55)	0.67

Online Table 2. Biomarkers predictive for successful up-titration of ACE-inhibitors/ARBs

	LOG(ODDS RATIO)	STANDARD ERROR	P-VALUE
INTERCEPT	-3.6472	3.2885	0.2674
NYHA CLASS	-0.0139	0.0424	0.7423
AETIOLOGY	-0.0508	0.1372	0.711
DM	0.4142	0.1419	0.0035
HYPERTENSION	0.2689	0.137	0.0497
RENAL DISEASE	-0.3537	0.177	0.0457
WEIGT	0.0112	0.0071	0.1168
SBP	0.011	0.0039	0.0051
DBP	0.0131	0.0064	0.0414
BMI	0.004	0.0235	0.8636
TOTAL CHOLESTEROL	0.0083	0.0288	0.7729
BUN	-0.0382	0.0118	0.0012
LVEF	0.0067	0.0097	0.4896
NT-PROBNP	<0.00001	<0.00001	0.7566
HB	0.0083	0.0271	0.7593
SODIUM	0.0266	0.0186	0.1521
GLUCOSE	0.0063	0.0204	0.7586
SERUM IRON	0.0026	0.0081	0.7469
FERRITIN	-0.0008	0.0013	0.5437
FT4	-0.0029	0.0084	0.7276
HBA1C	0.0155	0.0439	0.7231
ALAT	-0.0016	0.0045	0.7166
PURIA	-0.0026	0.0067	0.7045
GGT	<0.00001	0.0006	0.9853
ALKALINE PHOSPHATASE	-0.0035	0.0018	0.0542
TNI	-0.0008	0.0028	0.7706
PRO-ENK	-0.0011	0.002	0.5795
FGF23	0.0003	0.0003	0.2848
D DIMER	-0.0001	0.0005	0.7766
ST2	-0.0069	0.0125	0.5794
WAP4C	-0.0026	0.0707	0.9704
TLT 2 (NPX)	0.0604	0.1572	0.7007
TR (NPX)	-0.1612	0.121	0.1828
CASP 3 (NPX)	0.0061	0.0241	0.7992
CHI3L1 (NPX)	-0.0412	0.0657	0.5304
ST2 (NPX)	0.0264	0.119	0.8245
CURRENTLY SMOKING	-0.0218	0.0676	0.747

Online Table 3. Biomarkers predictive for successful up-titration of beta-blockers

	LOG(ODDS RATIO)	STANDARD ERROR	P-VALUE
INTERCEPT	-8.2129	4.9585	0.0977
SEX	0.9389	0.2712	0.0005
VALVULAR DISEASE	-0.2903	0.181	0.1088
PREVIOUS HF HOSPITALIZATION	0.2215	0.213	0.2984
HF DURATION	-0.0056	0.0142	0.6953
AF	0.3144	0.1853	0.0898
HYPERTENSION	0.3614	0.1824	0.0475
ALCOHOL	0.1454	0.2001	0.4676
STROKE	-0.5541	0.341	0.1042
PERIPHERAL ARTERY DISSEASE	-0.4903	0.3104	0.1142
COPD	-0.3261	0.301	0.2786
HEIGT	0.0307	0.0125	0.0145
WEIGT	0.0013	0.0048	0.7931
HR	0.0148	0.0041	0.0004
DBP	0.0055	0.0066	0.4046
PULMONARY CONGESTION	-0.0613	0.1004	0.5413
THIRD HEART TONE	-0.2145	0.3319	0.5181
NYHA CLASS	-0.0715	0.1287	0.5784
ORTHOPNEA	-0.3858	0.1994	0.053
TOTAL CHOLESTEROL	-0.1074	0.1145	0.3486
BUN	-0.0115	0.0185	0.5339
LVEF	0.0087	0.0128	0.4984
NTPROBNP	0	0	0.7205
SODIUM	0.0029	0.0125	0.8175
BNP	1.00E-04	2.00E-04	0.5945
TOTAL BILIRUBIN	-0.0093	0.0134	0.4871
LDL	-0.0709	0.1361	0.6025
HDL	0.0601	0.1793	0.7375
PHOSPHATE	0.3443	0.4525	0.4467
ALBUMIN	-0.0099	0.0166	0.5489
HEPC	0.002	0.0074	0.7853
FT4	0.0147	0.0205	0.4753
HBA1C	0.0609	0.0812	0.4535
ASAT	0.0041	0.0096	0.6674
ALAT	-0.0086	0.0121	0.4773
TSH	-0.0119	0.0367	0.7453
GGT	0.0019	0.0026	0.4656
ALKALINE PHOSPHATASE	-0.0011	0.0028	0.7024
TNI	-0.0031	0.0052	0.551
BIOADM	0.0058	0.0055	0.294
TROPONIN	-1.1956	1.596	0.4538
D DIMER	-0.0028	0.0012	0.0166
RAGE	-0.0389	0.102	0.7032
SYNDECAN1	-0.023	0.0644	0.7217
GDF15	0.0493	0.1299	0.7041
ST2	0.0112	0.0168	0.5052
PERIOSTIN	0.0412	0.0311	0.1859
CYSTATIN C	0	0	0.7222
NGAL	-0.001	0.0021	0.6395
OPG (NPX)	0.058	0.1722	0.7363
NOTCH 3 (NPX)	0.0912	0.2033	0.6535
PAI (NPX)	-0.0764	0.1101	0.4878

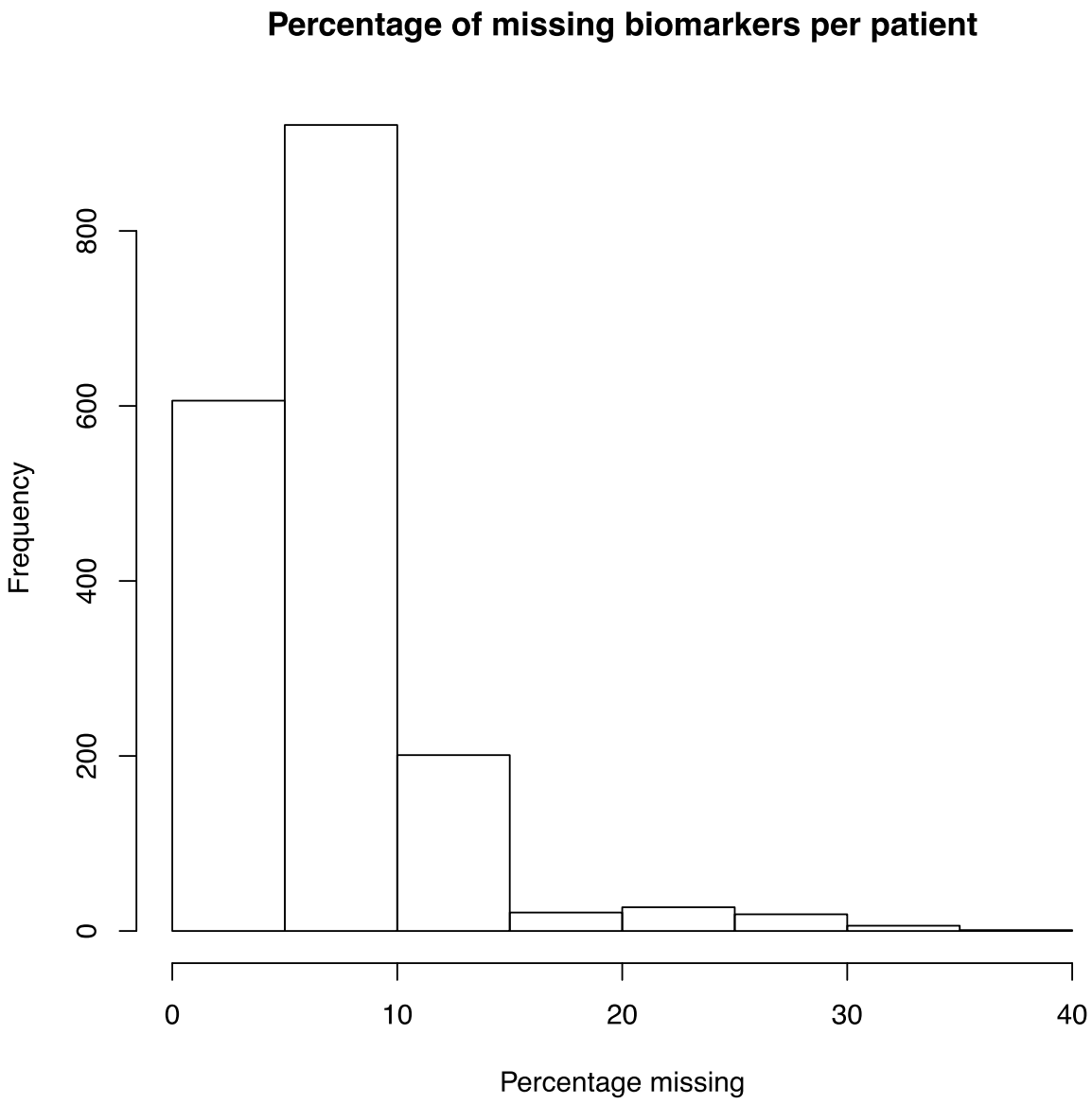
CCL24 (NPX)	0.1089	0.1072	0.3101
TR (NPX)	-0.1063	0.1813	0.5576
GDF 15 (NPX)	0.064	0.172	0.7096
SELE (NPX)	0.0494	0.1165	0.6716
AZU1 (NPX)	-0.1858	0.1519	0.2213
IGFBP 1 (NPX)	-0.1163	0.0687	0.0904
CHIT1 (NPX)	-0.0061	0.0116	0.6017
AP N (NPX)	0.0428	0.1468	0.7706
MMP 2 (NPX)	0.0963	0.2023	0.634
MB (NPX)	-0.2217	0.1616	0.1699
CPA1 (NPX)	-0.013	0.048	0.7863
CPB1 (NPX)	-0.1323	0.1076	0.2192
MMP 3 (NPX)	0.2828	0.2131	0.1843
PDGF SUBUNIT A (NPX)	-0.0639	0.0625	0.3068
TNF R1 (NPX)	-0.3701	0.2918	0.2046
CCL16 (NPX)	0.2036	0.1849	0.2707
PLATELET COUNT	0.0003	0.0009	0.7626
LEUCOCYTE COUNT	0.0644	0.0378	0.0883
CURRENTLY SMOKING	-0.2888	0.2763	0.2959
FORMERLY SMOKING	0.1726	0.1985	0.3847

Online Table 4. Biomarkers predictive for successful up-titration of MRAs

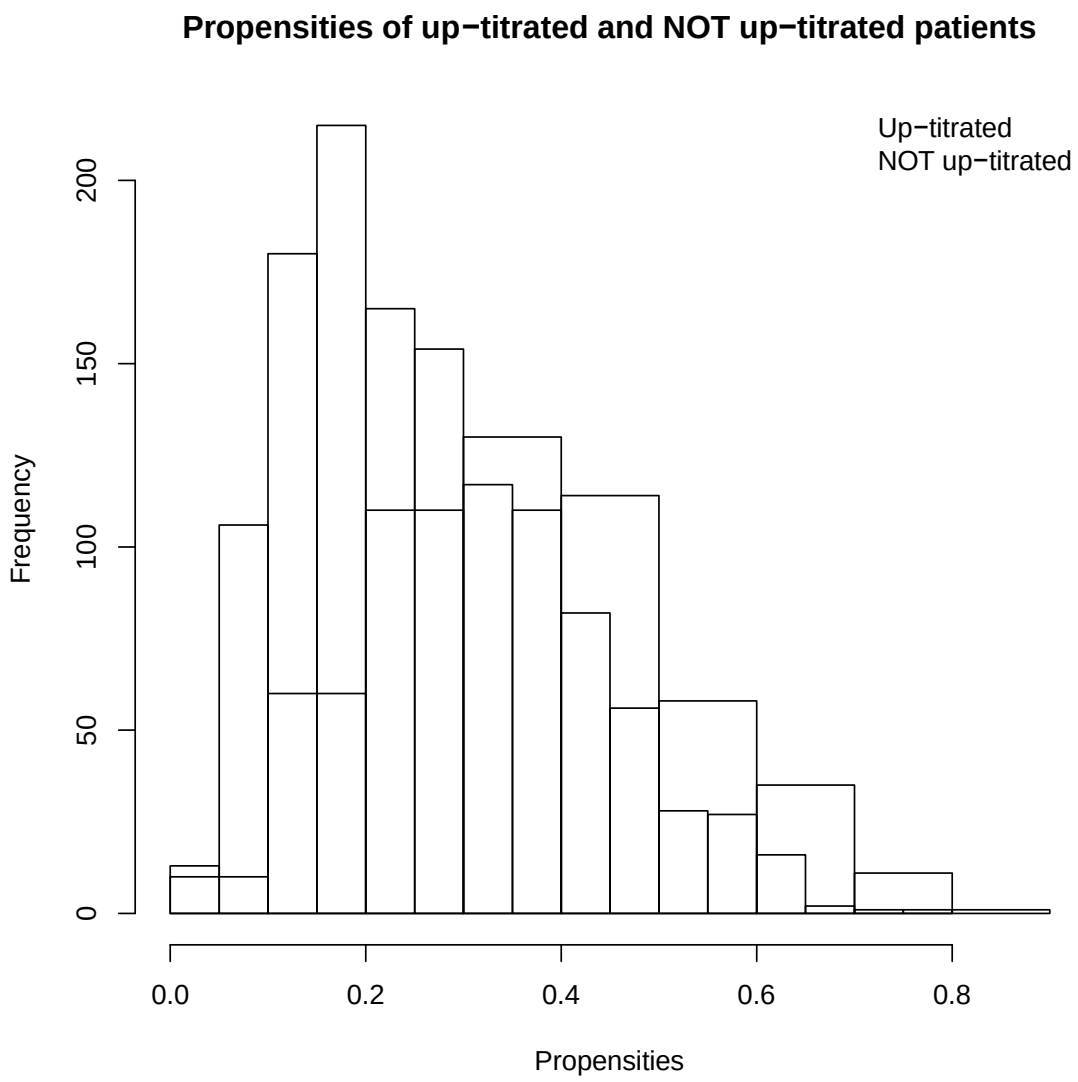
	LOG(ODDS RATIO)	STANDARD ERROR	P-VALUE
INTERCEPT	16.4541	8.9701	0.0666
SEX	-0.2191	0.2804	0.4345
RACE	0.8595	0.2745	0.0017
AGE	-0.0086	0.0097	0.3755
VALVULAR DISEASE	0.2993	0.1859	0.1074
HF DURATION	-0.01	0.0165	0.5468
NYHA CLASS	-0.1848	0.085	0.0296
DM	0.2491	0.2119	0.2398
ALCOHOL	0.042	0.1357	0.7572
CAD	-0.1493	0.1974	0.4492
RENAL	-0.2204	0.2867	0.4421
STROKE	-0.3654	0.356	0.3047
DEVICE THERAPY	0.2265	0.0698	0.0012
WEIGT	-0.0026	0.0107	0.8067
SBP	0.0002	0.0056	0.9717
DBP	-0.0079	0.0093	0.3948
HEPATOMEGALY	0.7995	0.2458	0.0011
THIRD HEARTTONE	0.7068	0.2794	0.0114
BMI	0.0504	0.0357	0.1578
HT	-0.0087	0.0233	0.7076
TOTAL CHOLESTEROL	-0.0483	0.0893	0.5884
SERUM CREATININE	-0.0055	0.0042	0.1897
LVEF	-0.0483	0.015	0.0013
NTPROBNP	0	0	0.5871
POT	-0.2773	0.1978	0.161
BNP	0	0.0001	0.7258
LDL	0.0261	0.0743	0.7252
HDL	-0.1594	0.2658	0.5485
SERUM IRON	-0.0035	0.0176	0.8441
HEPC	0.007	0.0119	0.5562
FT4	0.0043	0.0131	0.7413
HBA1C	-0.034	0.0885	0.701
ASAT	0.0002	0.0022	0.9389
TSH	-0.0031	0.081	0.9699
PURIA	0.0173	0.0149	0.2444
APHOS	-0.0027	0.0028	0.3326
PSAP B	0.015	0.0086	0.082
VEGFR1	0.7198	1.0027	0.4729
D DIMER	-0.0025	0.0013	0.047
GAL3	0.0161	0.0092	0.0794
NGAL	-0.0011	0.0023	0.6435
MMP 9 (NPX)	0.131	0.1126	0.2447
CD163 (NPX)	-1.022	0.2083	0
CNTN1 (NPX)	0.2651	0.2519	0.2926
CCL24 (NPX)	0.1579	0.0992	0.1116
DLK 1 (NPX)	-0.1563	0.1686	0.3539
SPON1 (NPX)	-0.2588	0.3273	0.4291
EPCAM (NPX)	-0.3062	0.1131	0.0068
AP N (NPX)	0.4819	0.2755	0.0802
JAM A (NPX)	0.1058	0.0894	0.2369
GAL 4 (NPX)	0.3914	0.1765	0.0266
IL 1RT2 (NPX)	0.4545	0.2864	0.1126
SHPS 1 (NPX)	-0.343	0.2266	0.1301
CPB1 (NPX)	-0.0693	0.0901	0.4416

CD93 (NPX)	-0.3831	0.2693	0.1549
PON3 (NPX)	0.022	0.0813	0.7866
RARRES2 (NPX)	0.2499	0.2887	0.3868
TNF R1 (NPX)	-0.0658	0.222	0.7668
PLATELET COUNT	-0.0032	0.0019	0.0958

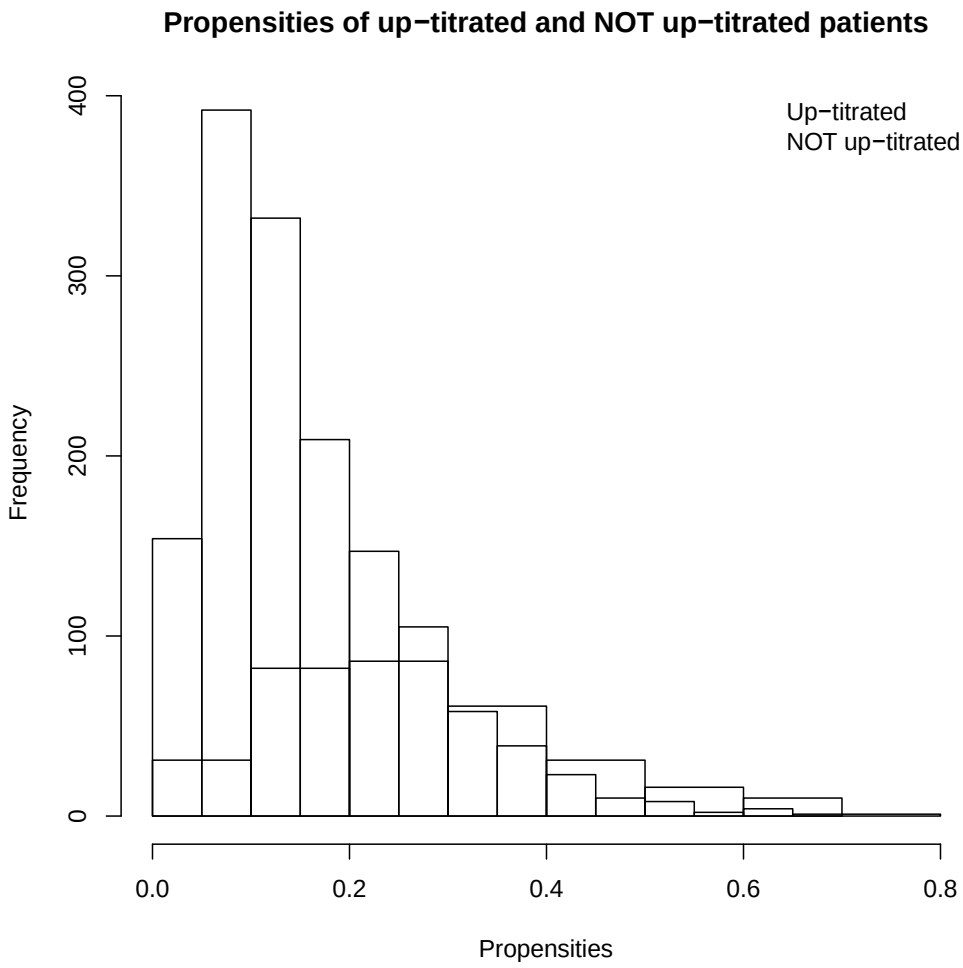
Online Figure 1.



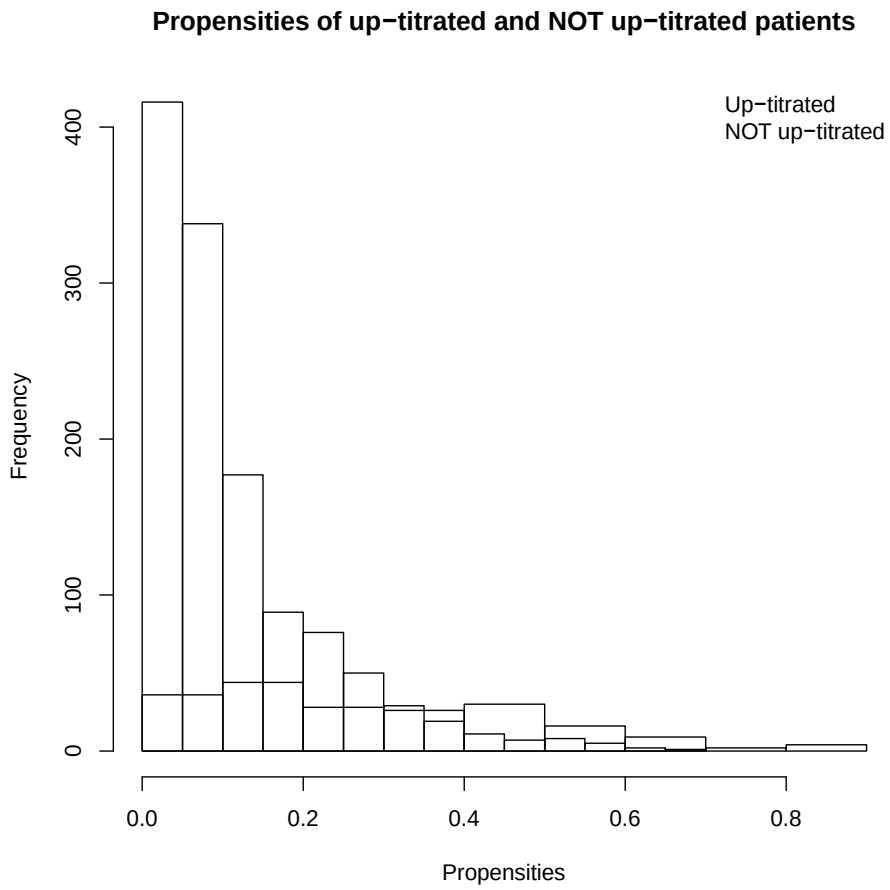
Online Figure 2. Probability (propensity) of successful up-titration of ACE-inhibitors/ARB's to >50% of recommended doses according to the sparse logistic regression model in patients who were successfully up-titrated and in patients who were not successfully up-titrated. The frequencies indicate how many patients had that propensity. The fact that the propensity distributions in the two treatment groups overlapped made correction for indication bias possible.



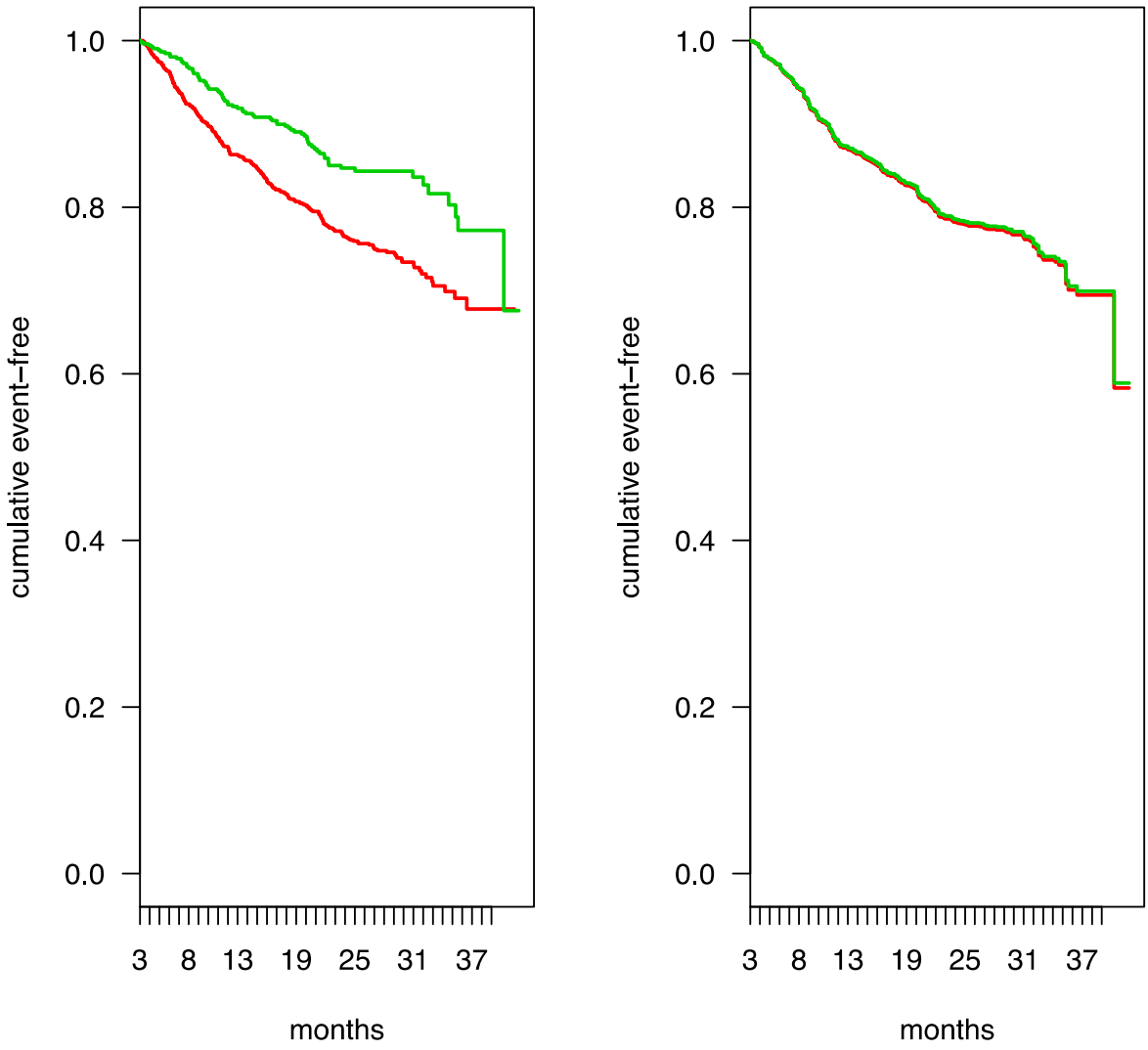
Online Figure 3. Probability (propensity) of successful up-titration of beta-blocker to >50% of recommended doses according to the sparse logistic regression model in patients who were successfully up-titrated and in patients who were not successfully up-titrated. The frequencies indicate how many patients had that propensity. The fact that the propensity distributions in the two treatment groups overlapped made correction for indication bias possible.



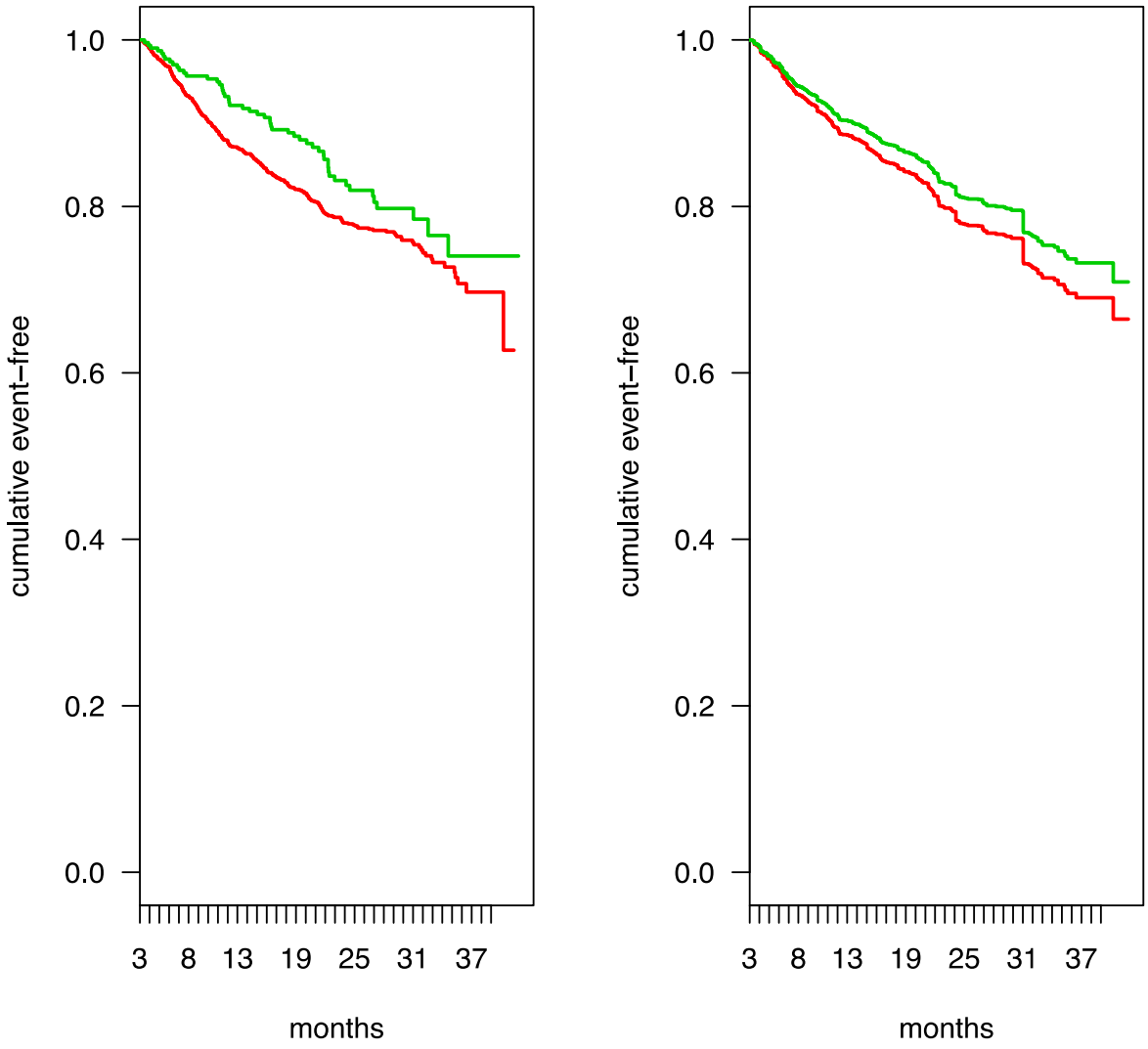
Online Figure 4. Probability (propensity) of successful up-titration of MRA's to ≥50% of recommended doses according to the sparse logistic regression model in patients who were successfully up-titrated and in patients who were not successfully up-titrated. The frequencies indicate how many patients had that propensity. The fact that the propensity distributions in the two treatment groups overlapped made correction for indication bias possible.



Online Figure 5. Panel A: Kaplan-Meier survival curves of patients who were successfully up-titrated (green) and of patients who were not successfully up-titrated (red) to >50% of recommended ACE-inhibitor/ARB dose. Panel B: Survival curves of patients who were successfully up-titrated (green) and of patients who were not successfully up-titrated (red) to >50% of recommended ACE-inhibitor/ARB dose, inversely weighted with the probability of the given treatment.



Online Figure 6. Panel A: Kaplan-Meier survival curves of patients who were successfully up-titrated (green) and of patients who were not successfully up-titrated (red) to >50% recommended beta-blocker dose. Panel B: Survival curves of patients who were successfully up-titrated (green) and of patients who were not successfully up-titrated (red) to >50% recommended beta-blocker dose, inversely weighted with the probability of the given treatment.



Online Figure 7. Panel A: Kaplan-Meier survival curves of patients who were successfully up-titrated (green) and of patients who were not successfully up-titrated (red) to ≥50% of recommended MRA dose. Panel B: Survival curves of patients who were successfully up-titrated (green) and of patients who were not successfully up-titrated (red) to ≥50% of recommended MRA dose, inversely weighted with the probability of the given treatment.